Curr Oncol Rep (2012) 14:91–96
DOI 10.1007/s11912-011-0204-x

NEURO-ONCOLOGY (M GILBERT, SECTION EDITOR)

Clinical Trial Design in Brain Metastasis: Approaches for a Unique Patient Population

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Published online: 26 October 2011

Abstract Clinical trials in brain metastases present challenges and opportunities unique to this patient population. With the increase in awareness and screening for brain metastases, smaller and often asymptomatic lesions are detected, creating the opportunity for trials of pre-irradiation chemotherapy. The goal of earlier intervention is advanced by studies to prevent brain metastases in high-risk populations. Sequencing of systemic chemotherapy with experimental chemotherapy in the context of a clinical trial requires collaboration between the investigators and the treating medical oncologists beginning ideally during design of the study. Adaptive randomization improves the efficiency of randomized trials in the brain metastasis population. Finally, collaborative efforts between patients and physicians with the support from patient advocacy groups will help advance the quality and the clinical trial options for patients with brain metastases.

Keywords Brain metastasis · Clinical trials · Clinical trial design · Chemotherapy · Systemic therapy · Randomized phase 2 · Adaptive randomization · Pre-irradiation chemotherapy · Chemoprevention · Primary prevention · Secondary prevention · Stratification · Stereotactic radiosurgery · Whole brain radiation therapy · Chemobrain · Leptomeningeal carcinomatosis · Blood-brain barrier · Patient advocacy

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Introduction

Clinical trial design for patients with brain metastases presents both opportunities and challenges. Historically few trials have been completed and most of those have been phase 2 studies or underpowered phase 3 studies. In addition, most of the studies have included a mixture of patients for which assessment of results in a particular histology has been difficult. The pioneers in these clinical trials and in particular those that evaluated the efficacy of chemotherapy as a single modality have come mainly from Europe [1–4]. Some of the early trials evaluated chemo-naïve patients whose initial presentation was with brain metastases [5–7]. In that time period, before the widespread use of screening mammograms, chemotherapy-naïve breast cancer patients for such trials were readily available.

Today, in the era of heightened awareness of breast cancer and the widespread use of mammographic screening, a patient whose initial presentation of breast cancer includes central nervous system (CNS) metastasis is rare, and trials of chemo-naïve patients would be essentially impossible. Other cancer types, however, lend themselves more readily to trials of chemotherapy in brain metastases. Patients with diseases such as non–small cell lung cancer and renal cancer, where screening is not standard, can present with brain metastases at the time of diagnosis, allowing investigators to design clinical trials that evaluate brain metastases early in the patient's course. Therefore, clinical trials in patients with brain metastases should in general be limited to a single histology. Exceptions to this guideline could include phase 1 trials or trials of non-chemotherapeutic interventions such as surgery. Furthermore, stratification becomes increasingly important as

biologically and clinically distinct subgroups of brain metastases patients become evident. Extensive analyses of patients with newly diagnosed brain metastases from lung and breast cancer have allowed investigators to select and to stratify patients into groups expected to differ substantially in their outcomes [8•, 9••]. This review will explore challenges in the design of clinical trials of brain metastases with the focus on systemic therapies.

A Changing Landscape

As suggested above, the population of patients with brain metastases is evolving significantly. Given the rapidly expanding number of treatment options for systemic disease, brain metastasis tends to be a later event in the course. The biology and indeed the phenotype of the cancer may change from that of the original diagnosis. One study of breast cancer patients documented a significant change in hormone receptor status and HER2-neu status between primary lesions and metastases in the same patients [10]. "Screening" for brain metastases is becoming more common, particularly in malignancies such as breast cancer, leading to earlier diagnoses, smaller lesions, and fewer lesions. Thus, the clinical indications for surgical resection (eg, relief of mass effect) have decreased steadily over the past 5–10 years. As a result, the clinical trial schema using preoperative chemotherapy with tissue-correlative studies followed by post-operative treatment in brain metastasis patients has become nearly impossible to accrue in a timely fashion.

Conversely, the shift toward earlier diagnosis leads to more patients receiving stereotactic radiosurgery (SRS). This shift in turn represents an opportunity in clinical trial development to explore alternatives to whole brain radiation therapy (WBRT) in secondary prevention (prevention of emergence of new brain metastases after definitive treatment of index lesions) strategies as exemplified by several current clinical trials; examples include studies that use RO4929097 or sunitinib (ClinicalTrials.gov Identifiers: NCT01217411; and NCT00910039 and NCT00981890, respectively). Finally, some clinical trials have begun to explore the possibility of primary prevention (prevention of brain metastases in patients without history of brain metastases) (eg, ClinicalTrials.gov Identifiers: NCT00820222, NCT00639366) [11••]. Further trials in these settings would ideally lead to randomized trials that compare WBRT to chemotherapy as post-SRS management—admittedly a difficult randomization for patients and physicians to accept. A more likely scenario would compare two agents or one agent against placebo as chemopreventative drugs in the primary prevention setting. Examples of phase 3 trials include one which compares lapatinib and capecitabine to trastuzumab and capecitabine for the prevention of brain metastases in women with HER2+ metastatic breast cancer (ClinicalTrials.gov Identifier: NCT00820222) and another which tests prophylactic cranial irradiation in HER2+ metastatic breast cancer (ClinicalTrials.gov Identifier: NCT00639366).

Extensive Pretreatment

Brain metastases typically present late in the course of a patient's illness. Thus, the patient may have received multiple chemotherapy regimens and may have end-organ toxicities that include neuropathy, bone marrow compromise, chronic fatigue, and anorexia as well as a sense of emotional fatigue—"I'm tired of fighting." "Chemobrain" is a well-known phenomenon in such patients [12]. All of these factors make it difficult for patients to meet eligibility criteria for a study of chemotherapy in brain metastases. In addition, the evaluation of toxicities of the study agent may be difficult to distinguish from subtle pre-existing conditions, especially in the assessment of neurocognitive toxicities. An estimated 90% of patients with brain metastases have cognitive impairment at the time of diagnosis [13]. Therefore, careful patient selection in the design of eligibility criteria is crucial to the success of a brain metastasis trial.

Given the wide availability of clinical trials for systemic disease and the interest of patients and pharmaceutical companies in cancer clinical trials, patients with brain metastases may have received agents with mechanisms of action similar or identical to the agent of interest in a clinical trial thus making the patient ineligible for a study. A solution for this problem is to allow the enrollment of an exploratory cohort of patients who have received a drug of the same class or even the same agent, perhaps on a schedule different from that used previously for treatment of the patient's systemic disease. The study would be powered according to the main cohort of patients (ie, no previous treatment with the same class of agent) so that inclusion of the smaller cohort would not affect the primary end points of the trial.

Concurrent Systemic Disease

A major barrier to the success of clinical trials in brain metastasis is the need to control both systemic and CNS disease. The success of systemic therapies for most cancers usually depends on agents which do not cross the blood–brain barrier (BBB) [11••, 14]. As more such agents become available, more patients will present with brain metastasis in the setting of controlled systemic disease. For most experimental drugs considered for chemotherapy trials

in brain metastases, no data will exist to attest to the safety of the new agent combined with the systemic regimen needed to maintain systemic disease control. For the patient, investigator, scientific review committee, and the institutional review board, the discontinuation of the successful systemic regimen is problematic. Indeed, a recent study of WBRT and stereotactic radiosurgery followed by randomization to no drug or one of two specified chemotherapy regimens (ClinicalTrials.gov Identifier: NCT00096265) closed prematurely due to poor accrual based on a reluctance of investigators to delay standard chemotherapy temporarily (Paul Sperduto, Personal communication).

Several possible strategies could address this challenge. First, an agent with BBB penetration and systemic efficacy represents an attractive molecule for clinical trials of brain metastases. An example of this class of agents is the epothilones [15, 16]. Such agents, however, are uncommon. Second, some agents do have phase 2 data which combine the agent in question with several systemic regimens. In these situations, a patient could enter the study and receive the study drug within a combination for which phase 2 doses exist. One ongoing pilot clinical trial for patients with one to three brain metastases (ClinicalTrials.gov Identifier: NCT00910039) uses SRS followed by sunitinib in lieu of whole brain radiation therapy for secondary prevention of further brain metastases. For this particular agent, multiple trials have combined systemic agents with sunitinib. These combinations are allowed as regimens on the trial, thus giving patients and investigators the opportunity to continue a regimen that is controlling the systemic disease while participating in the trial. This strategy, however, is applicable to a limited number of agents and adds considerable heterogeneity to the chemotherapy administered. For certain subgroups of patients whose systemic disease is controlled by selected agents, the addition of an experimental agent should be allowed. For example, patients with breast brain metastases whose systemic disease is controlled with hormonal therapy or by trastuzumab should not be excluded from protocol entry unless the experimental agent has some evidence of overlapping toxicity with the experimental agent. Alternatively, a safety run-in cohort of patients (eg, six patients) could be accrued with additional safety testing such as, for instance, echocardiograms for patients receiving trastuzumab if there was a concern for cardiac toxicity.

Concurrent WBRT and Chemotherapy

Some experimental drugs may be investigated as radiosensitizing agents in trials of WBRT with the goal of enhancing the CNS control afforded by WBRT. The selection of such agents for this trial design ideally is based upon preclinical data that demonstrates radiosensitization and the ability of the drug to cross the BBB. Some agents, for example inhibitors of DNA damage repair, would be expected to have little or no activity alone. Therefore, the patient would generally be placed on (or resume) a systemic chemotherapy regimen soon after the completion of radiation therapy. The assessment of efficacy for CNS control or response should occur soon after the completion of WBRT—eg, 1 month—in order to assess the efficacy of the CNS-directed therapy apart from that of the systemic regimen, if any.

For an agent that might be expected to have systemic activity in addition to radiosensitizing properties, however, the temptation is to design the study with continuation of that agent until progression. If the study *mandates* the continuation of a specific post-radiation regimen, however, it risks poor accrual for the reasons mentioned above: the understandable reluctance of the patient and/or the treating physician to withhold a regimen that was controlling systemic disease.

One approach to this dilemma is to allow the experimental agent to continue for a limited period (eg, 1 month) of time after WBRT is complete at which time restaging of both CNS and systemic disease would be repeated. Patients with controlled systemic disease at that time could be offered the option of continuing the experimental regimen until the time of progression in the brain or the systemic compartment. The most appropriate primary end point for such a trial would be the intracranial efficacy measured either by response rate at a defined and early landmark such as 1 or 2 months after the completion of radiation therapy. Critical for the success of such a study is the endorsement of the patient's treating medical oncologist as well as the radiation oncologist. It would be important to educate the treating physicians that the protocol allows but does not mandate continued experimental therapy.

Unexpected Behavior of the Blood–Brain Barrier

The decision to move forward with a clinical trial in brain metastases, and indeed, the likelihood of obtaining funding and regulatory approval stands largely on preclinical data. For trials of brain metastases, these data would ideally verify that the compound crosses the BBB and that it has efficacy against the tumor. While efficacy against the tumor is an obvious requirement, BBB penetration is more complex. Elegant studies have demonstrated that the complexities of CNS pharmacokinetics depend on a myriad of factors including, but not limited to, molecular size, lipophilicity, protein binding, the presence of efflux pumps, and the striking heterogeneity within the tumor itself [14, 17]. Furthermore, the BBB integrity may change during the

course of the study. For example, in a trial of WBRT combined with an experimental agent, traverse of the agent through the BBB may improve during the course of WBRT due to radiation-induced BBB disruption [18].

While the BBB excludes most molecules larger than 180 daltons, ipilimumab has a weight of 145 kdaltons—800-fold heavier! This molecule, however, has clear activity against melanoma brain metastases [19, 20, 21•]. Presumably this activity represents, in part, the disruption of the BBB in the setting of brain tumors [14]; however, the activity may also be due to blockage of CTLA-4 in peripherally circulating lymphocytes that then results in increased tumor lymphocyte penetration. The unexpected activity of ipilimumab led to the Cytokine Working Group to study ipilimumab in patients with brain metastases with the finding of intracranial disease control in 18–24% of patients [22]. The Italian Network for Tumor Biotherapy will extend these findings in a trial of ipilimumab and fotemustine that includes patients with pretreated, asymptomatic brain metastases with brain PFS as a secondary end point [23]. The ideal measure of drug activity in the brain is the assay of target modulation within the tumor in the resected tissue of preoperatively treated patients [24]. Alternatively, sophisticated imaging modalities may provide valuable surrogate pharmacodynamic data [25]. Therefore, given the sometimes unpredictable behavior of the BBB, clinical trial design in patients with brain metastases would ideally examine BBB pharmacokinetics with the aid of tissue (when available) or imaging.

Special Circumstances

Patients with leptomeningeal disease (LMD) have limited treatment options, a poor prognosis, and few clinical trial options. The majority of clinical trials exclude patients with LMD. For studies of local therapy such as surgery and SRS, this exclusion is appropriate. WBRT and most clinical trials of WBRT also do not address LMD. Brain metastasis studies, however, that use chemotherapy as a single modality or WBRT trials that include an agent with expected antitumor activity could enroll such patients. While designing a brain metastasis trial with end points and sample sizes that address the larger population with parenchymal brain metastases, one could allow entry of a small exploratory cohort of patients with LMD. These patients could then receive an experimental agent, and some efficacy and toxicity data in this unique patient population would be obtained.

Several additional situations deserve mention. Patients with unirradiated brain metastases, especially if small with minimal or no symptoms, should be eligible for clinical trials of chemotherapy. Multiple studies have demonstrated that CNS response rates in previously unirradiated brain metastases approximate those obtained in the systemic disease [1, 5, 7, 26, 27]. Additional ongoing clinical trials include a study of irinotecan and iniparib in patients with triple-negative (ER, PR, and HER2 negative) breast cancer brain metastases (ClinicalTrials.gov Identifier: NCT01173497), as well as studies in lung cancer, renal cell cancer, and melanoma (ClinicalTrials.gov Identifiers: NCT00800202, NCT00814021, and NCT01378975, respectively). Finally, the vast majority of early-phase clinical trials of experimental agents in oncology exclude patients with brain metastases. Although the scope of this manuscript focuses on the design of trials for brain metastases, the entry criteria for non–CNS-specific trials should allow entry of this patient population [28, 29, 30•]. Investigators involved in the design of brain metastasis trials should continue to advocate for this eligibility [28, 29, 30•].

Specific Study Designs

While a statistical analysis of all clinical trial designs is beyond the scope of this manuscript, several clinical trial designs can guide the efficient study of brain metastases. Window-of-opportunity trials take advantage of a "window of opportunity" in a patient's disease—a limited time in the course of the patient's treatment during which a clinical trial can yield data not otherwise obtainable. For example, patients with small or minimally symptomatic brain metastases have a window of time before standard therapy—SRS or WBRT—must commence. Because chemotherapy has greater efficacy before rather than after radiation [1, 5, 7, 26, 27], this window affords an attractive time period in a patient's illness in which to test novel agents [31]. The delay in standard therapy during the conduct of window studies does not appear to compromise patient outcomes [31].

Another example of a window trial in brain metastases is the use of chemotherapy following SRS in the window between SRS and WBRT. Although perhaps controversial, many investigators consider WBRT to be a standard of care following SRS based on several clinical trials [32, 33]. Therefore, a trial of chemotherapy in the window between SRS and WBRT would test the efficacy of chemotherapy as a strategy to delay the need for WBRT.

A study that combines WBRT with an agent anticipated to have systemic activity could also represent a window trial. In the window between completion of WBRT and resumption of chemotherapy, the experimental agent could be continued with the end point of progression-free survival in both the CNS and the systemic compartments. As with all trials that involve the potential delay in resumption of an effective systemic regimen, the success of the study

depends on close collaboration between the investigator and the treating medical oncologist. Ideally, this collaboration would begin during the design phase of the study in order to facilitate accrual once the study begins.

Randomized trials in brain metastases can take several forms. Over the past 5–10 years randomized phase 2 trials, although less statistically robust than phase 3 trials, have become more popular and indeed have become a recommended strategy by the National Cancer Institute [34•]. The randomized phase 2 design essentially "bundles" two or more phase 2 trials into one study with the advantage that the entry criteria, methods, institutions, and other factors are uniform between the arms [35]. Some randomized phase 2 trials contain a control arm. For example, one developing randomized phase 2 trial (RTOG 1118) for patients with multiple brain metastases tests the addition of each of several experimental agents to WBRT but also has an arm of WBRT alone. While the randomized phase 2 trial is not designed to compare the arms to each other or to a control therapy, a standard treatment arm helps to ensure that biases due to patient selection or other factors do not create false interpretations of the data.

Adaptive randomization can make clinical trials more efficient in reaching end points with fewer patients than required with conventional randomization [36]. Examples of two such designs in oncology include the I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2) and the BATTLE trials (Biomarker-Integrated Approaches of Targeted Therapies for Lung Cancer Elimination) [37, 38]. Adaptive designs use data from the trial as it progresses in order to adapt the conduct of the trial to accrue more patients to the arms that, based on the emerging data, appear to be more efficacious [35]. This approach can include several adjustments such as modification of the dose in a phase 1 trial (eg, continual reassessment method) or the discontinuation of arms or of doses [34•, 35]. In RTOG 1118, arms in which the 1-month post-WBRT response rate falls below a predetermined threshold will be dropped. Those that exceed a given threshold at 3 months post-WBRT will be considered for further testing perhaps in a phase 3 trial. Additional arms with new experimental agents to be combined with WBRT will be added in order to allow the trial to test many agents in a continuing trial over the span of years.

Conclusions

Despite challenges unique to patients with brain metastases, clinical trials are clearly feasible and have produced improvements in quality of life, CNS progression, and, in some prospectively analyzed subgroups, survival [39]. One of the challenges in collaboration in brain metastasis trials is the transition in providers at the time of diagnosis of brain metastases. The focus of treatment shifts from the medical oncologist to the radiation oncologist, a transition which, at the time of the event, adds to the patient's stress [40]. Clinical trial entry can be challenging as it usually requires multidisciplinary engagement with the radiation oncologist perhaps having to present to the patient a WBRT-chemotherapy trial. Furthermore, the prospect of discontinuing systemic therapy, the one part of the treatment plan that has not failed, in order to enroll on a clinical trial, takes trust and courage on the part of the patient. Patient support and advocacy is an active element in the support of patients, particularly women with breast cancer. An example of such support is the excellent website brainmetsbc.org, which offers patients detailed information on brain metastases and an extensive listing of clinical trials in brain metastasis not only from breast cancer but from other primary sites as well [41]. As the number of experimental agents and devices increases, and available resources contract, the proper design of clinical trials will require increasing collaboration between physicians, research nurses, statisticians, administrators, and regulatory agencies.

Disclosure No potential conflict of interest relevant to this article was reported.

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